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UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

THE JOHNS HOPKINS UNIVERSITY, a Maryland corporation, BAXTER HEALTHCARE CORPORATION, a Delaware corporation, and BECTON DICKINSON AND COMPANY, a New Jersey corporation,	:	Case No. 94-105 RRM
Plaintiffs,	:	
v.	:	
CELLPRO, INC., a Delaware corporation,	:	
Defendant.	:	

DECLARATION OF DR. KENT HOLLAND

DECLARATION OF DR. KENT HOLLAND

I, KENT HOLLAND, M.D., do hereby declare:

1. I am an Associate Professor of Medicine in the Emory University Medical School and am the Director of the Hemapheresis Center of the Bone Marrow Transplant (BMT) Program of the Emery University Hospital. A copy of my curriculum vitae is attached hereto as **EXHIBIT A**.

2. I am well acquainted with the capabilities of CellPro's CEPRATE® SC stem cell concentrator. My familiarity with that device is based on: (a) Having been trained in its operation; (b) having read widely in the scientific and technical literature about its capabilities; (c) having worked with the device on a regular basis during the past five years (approximately); (d) having performed stem cell transplant procedures on approximately 75 to 100 human patients using suspensions prepared with the device; and (e) being currently involved in clinical trials of new therapies that utilize the CEPRATE® SC stem cell concentrator.

3. Before CellPro's CEPRATE® SC stem cell concentrator became

available, the standard technique for the preparation of suspensions for use in bone marrow transplantation was unpurified "buffy coat" progenitor cell transplantation (hereinafter "buffy coat PCT"). That technique involved separation of bone marrow components by centrifugation, recovery of the "buffy coat" component (which contained not only stem cells but also a variety of other cells, some of which were unnecessary to the goal of achieving safe and rapid long-term engraftment in a myeloablated patient, and potentiallly detrimental to the goal of achieving long-term survival), and intravenous injection of the "buffy coat" cells into the patient. Usually, and always in autologous settings (that is, when the suspension was prepared from the marrow of the intended recipient), the recovered "buffy coat" component had to be cryopreserved (i.e., frozen), and this required DMSO, a cryoprotectant, to be added to the suspension. While DMSO enhanced the cells' ability to survive the freezing-and-thawing cycle, DMSO was also toxic to the patient. At the levels required for buffy coat PCT therapy, DMSO could cause severe and potentially fatal cardiopulmonary side effects, including acute respiratory distress syndrome and cardiac arrhythmia. The buffy coat PCT suspension was often treated with chemotherapeutic drugs ("purging") in an effort to eliminate certain undesirable cells (such as, in the autologous

setting, malignant cells). The chemotherapeutic drugs increased the toxicity of the suspension because the selectivity of the chemotherapeutic drugs was imperfect, and those drugs were prone to kill or compromise the viability not only of the target cells but also of the normal hematopoietic stem cells themselves. This latter effect would generally result in prolonged periods of aplasia following transplantation which significantly increased the risk for morbidity and mortality above that observed with the use of the CEPRATE®-isolated hematopoietic stem cells.

4. The advent of the CEPRATE® SC stem cell concentrator made it possible to perform a therapeutically effective stem cell transplantation with far less risk of toxic side effects compared to buffy coat PCT. The CellPro device's efficiency in selecting the cells which are necessary for long-term durable engraftment, while leaving behind undesirable cells, makes it feasible to transplant a far smaller volume of cells than with buffy coat PCT; and while DMSO is still used as a cryoprotectant with the CellPro device in the autologous setting (and sometimes in the allogeneic setting), the volume of DMSO needed is much less than with buffy coat PCT. That procedure typically required the transplantation of a suspension of as great as one liter in volume, and the volume of

DMSO needed for cryoprotection was typically about 10% of that volume (i.e., about 100 ml of DMSO for a 1-liter suspension). The CellPro CEPRATE® SC device, in contrast, provides a highly enriched stem cell suspension in a volume so small that only a few drops of DMSO are needed to cryoprotect it; and at this comparatively low level DMSO poses far less of a toxicity problem to the patient.

5. In addition to making it possible to prepare a transplant suspension with lower toxicity than a buffy coat PCT suspension, CellPro's CEPRATE® SC stem cell concentrator produces a suspension that typically takes far less time than a chemotherapy-treated buffy coat PCT suspension takes to achieve restoration of the patient's immune-system function. In the chemotherapy treated buffy coat PCT therapy, the time interval between transplant and restoration of hematopoiesis function was, typically, on the order of 30 to 60 days; and in the meantime the patient was at great risk of death from overwhelming infection. When a suspension prepared by the CEPRATE® SC device is used, the typical time to achieve hematopoiesis recovery is far shorter -- typically 12 to 20 days -- and the risk to the patient of death from infection is significantly reduced.

6. For the foregoing reasons, CellPro's CEPRATE® SC stem cell concentrator is markedly superior to the prior (buffy coat PCT) technology for preparing a stem cell transplant suspension. For tumor-purging, the CellPro therapy has supplanted chemotherapy treated buffy coat PCT. Furthermore, the latter is no longer a realistically available treatment option in the United States, as the major chemotherapeutic agent used in buffy coat PCT tumor purging is no longer available in the U.S.

7. For some categories of patients with terminal hematopoietic malignancies (e.g. leukemia), there never was any transplant option, at all, until the advent of the CellPro CEPRATE® SC device. For example, I am currently participating in a clinical study using parents as donors for their children and young teenagers with acute leukemias who need stem cell transplants to survive but who have no suitable related or unrelated histocompatibility-matched donor available who is more than half-matched. Before the advent of the CellPro device, such patients invariably failed to survive, even with transplantation. The degree of tissue-mismatching was so great that patients would invariably succumb to graft failure, graft-versus-host disease or related complications. Now, with the CellPro device, it is possible in many cases to prepare a

transplant suspension from the marrow and/or peripheral blood obtained from the patient's parent with sufficient T-cell depletion to prevent fatal GVHD. In a pilot study in children, we achieved survival rates in the range of 30 to 40% for these patients who underwent haploidentical transplantation using parental donor cells manipulated with the CEPRATE® device. Before, these patients had no treatment option at all; they were not transplant candidates and, without transplantation, they typically succumbed to leukemia within 3 to 6 months after diagnosis.

8. I am also currently involved in clinical trials involving half-matched parents as donors for young adult (age 20-45) leukemia patients. This study is too new for success-rate data to be available; but here again, the category of patients is one for which there was no treatment option prior to the advent of the CellPro device.

9. I am also currently involved in clinical trials involving adult lymphoma patients who require autologous transplantation with tumor-cell purging. For these patients, such transplantation is potentially curative. The use of the CEPRATE® device allows for the removal of contaminating lymphoma cells which may improve the

patient's overall long-term survival benefit.

10. I am also involved in a study which aims to further reduce the severity of GVHD reactions using a second-generation CellPro device which, in the first step, enriches for stem cells and, in the second step, uses a different antibody to deplete T lymphocytes. This trial was instituted approximately three months ago for children with leukemia and other blood malignancies.

11. The CellPro CEPRATE® SC stem cell concentrator is the only immunoseparation device available which has FDA approval for human bone marrow transplantation. While I am aware that other companies (including Baxter, AIS, and Amgen) have or have had stem cell immunoseparation devices in development, I am aware of none others that have been FDA-approved. As for AIS, I understand that attempts to develop the product have been abandoned. I am unaware that the Amgen device is available for clinical use. Baxter's Isolex device, according to what I have heard and read about it, lacks sufficient demonstrated T-cell depletion capability that I would judge it to be practical for my child and young-adult studies even if the device were FDA-approved.

12. Even if the Baxter Isolex device (or another non-FDA-approved device) were technically suitable for my studies, it would be a considerable hardship for our bone marrow transplant program to switch over from the CellPro device to such other device. Introduction of a new immunoseparation device would require starting over from scratch, which would require mobilization of substantial personnel and financial resources. In addition, even if (for example) Baxter's device were offered to me tomorrow, I estimate that it would take somewhere on the order of nine months to a year to get studies underway using it. In addition of the time it would take to get a user agreement and a protocol agreed upon with Baxter, I believe several months of training time would be needed before I and my staff would have a level of experience and proficiency with the Isolex device that would begin to duplicate the level of experience and proficiency we now have in the use of the CellPro device. In addition, I would need to seek and obtain protocol approval from my university and then from the FDA. Meanwhile, progress in exploring new therapies would be retarded and desperately sick patients, who might be helped by the therapies under study, would perish.

13. Even if use of the CellPro CEPRATE® SC device were not

enjoined, or even if an injunction were fashioned which made generous exceptions for use of the device to explore new therapies, still the fact that the device is "under a legal cloud" has, in my view, a chilling effect on medical research. In addition to patients' worries over whether the device which is planned to be used for their treatment will remain available, investigators themselves must be worried about (a) whether studies involving the CellPro device will be interrupted for legal reasons and (b) whether it will prove to be a waste of precious time and resources to perfect new therapies centered on a device which, despite its technical merits and despite its unique FDA-approved status, might not remain available long-term.

14. For the foregoing reasons, it is my belief that there is a vital public interest in preserving the availability of the CellPro CEPRATE® SC stem cell concentrator for therapeutic uses, and related research uses, in the United States. Its removal from the U.S. market would effectively remove potentially life-saving therapy from patients who cannot afford to travel abroad for treatment. Its removal from the U.S. market would compromise the welfare of other stem cell transplant candidates, for whom it affords a treatment option superior to buffy coat PCT. Moreover,

the legal cloud of doubt over whether and to what extent it may be used in the United States hampers the willingness of medical researchers to use it to pursue new and potentially lifesaving therapies.

I declare under penalty of perjury that the foregoing is true and correct.

Executed at Atlanta, Georgia, this 21 day of March, 1997.

KENT HOLLAND, M.D.

Curriculum Vitae

H. Kent Holland, M.D.

Associate Professor of Medicine
Director, Hemapheresis Center
Bone Marrow Transplant Program, Department of Medicine
Emory University School of Medicine

Education: Duke University, B.S.E., 1978
Southwestern Medical School, Dallas, TX, M.D., 1982
Cornell University Medical Center, Department of Internal Medicine, Intern and Residency, 1982-85.
John Hopkins School of Medicine,
Sr. Clinical Fellow in Hematology and Oncology, 1985-88

Academic Appointments:

Johns Hopkins School of Medicine, Assistant in Oncology, 1988-89
Johns Hopkins School of Medicine, Instructor in Oncology, 1989-91
Johns Hopkins School of Medicine, Assistant Professor of Medicine, 1991
Emory University, Division of Hematology and Oncology, Assistant Professor, 1991-95
Emory University, Division of Hematology and Oncology, Associate Professor, 1995-
Emory University Hospital, Director, Hemapheresis Center, 1992-

Honors and Professional Memberships:

Tau Beta Pi (National Engineering Scholastic Society), 1977
Alpha Omega Alpha, 1982
Active Member, American Society of Clinical Oncology, 1991
Active Member, American Society of Hematology, 1995
Active Member, American Association of Blood Banks, 1996
Active Member, International Society for Experimental Hematology, 1996
Active Member, American Society for Blood & Marrow Transplant, 1996
Diplomat, American Board of Internal Medicine, Board Certification, 1985
Diplomat, American Board of Internal Medicine, Board Certification, Subspecialty of Medical Oncology, 1987
Diplomat, American Board of Internal Medicine, Board Certification, Subspecialty of Hematology, 1988

Publications: Author or co-author of 32 research articles in professional journals
Author or co-author of 58 abstracts
Author or co-author of 3 book chapters